Institution: King's College London (KCL)

Unit of Assessment: UoA4 – Psychology, Psychiatry & Neuroscience

Title of case study: 24: Genetic testing for motor neurone disease improves diagnosis and care

1. Summary of the impact

Genetic research at King's College London (KCL) has had significant impact on the current and future care of people with motor neurone disease (MND). KCL researchers discovered several MND-causing genes, which have been taken up by diagnostic and research laboratories throughout the world. This has improved early diagnosis and predictive gene testing in high-risk families and enabled children to be born free of MND by pre-implantation genetic diagnosis. Research laboratories in academia and industry have used mutant genes in cellular and animal models to identify fundamental disease mechanisms and disease-critical pathways to advance drug discovery for this fatal disease.

2. Underpinning research

Motor neurone disease (MND) (also known as Amyotrophic Lateral Sclerosis ALS) is caused by the degeneration of motor neurons in the brain and spinal cord. Muscle weakness begins in one limb but spreads relentlessly until patients are unable to walk, feed or toilet themselves, talk and eventually breathe. MND is the most common reason that people seek euthanasia. Every year 1,200 people in the UK will develop MND. There is no effective treatment and death occurs on average 3 years after symptom onset. MND is familial in 10% of cases, passed down through the generations, and a genetic basis for sporadic MND is increasingly recognised.

Researchers at Institute of Psychiatry, King's College London (KCL) led by Professors of Neurology Christopher Shaw (1995-present) and Ammar Al-Chalabi (2000-present) have made a major contribution to the discovery of MND genes. Their biological studies on mutant MND genes have generated novel insights into disease mechanisms driving forward drug discovery.

SOD1: In 1995, KCL researchers identified many novel mutations of SOD1, which accounts for 20% of familial and 3% of sporadic disease. They were the first to show that mutations occurred across all regions of the gene and protein, correctly challenging the view that mutations knocked out protein function (1), and launched a website collating mutations in all known MND genes.

TDP-43: KCL researchers were the first to describe mutations in TAR DNA binding protein gene in MND and show that these were neurotoxic. TDP-43 was identified in 2006 as a major protein included in 95% of MND and 60% of cases of Frontotemporal Dementia (FTD), but was dismissed by influential researchers as "cellular junk". However, in 2008, KCL researchers reported that some familial and sporadic MND cases carried TDP-43 mutations, which caused the proteins to fragment and become toxic to spinal cord neurons (2). KCL researchers and their collaborators have successfully replicated MND pathology in neurons grown from stem cells reprogrammed from patient skin cells (3). They have made great progress in exploring the toxic mechanisms in a range of cellular and animal models and are now working with pharmaceutical companies on a drug discovery programme.

FUS: In 2003, KCL researchers identified a region on chromosome 16 that contained a gene causing MND (4). In 2009, they identified it as Fused in Sarcoma (FUS). Mutations in FUS account for 3% of familial MND cases (5). KCL research in cells, animal and human patient tissues showed that mutant FUS accumulates in the cell body and is toxic to motor neurons.

ALS-FTD2 and C9ORF72: In 2006, KCL researchers were the first to discover that a region on Chromosome 9 contained a gene causing familial MND and FTD (6). In 2010, they demonstrated that the same region was also strongly associated with sporadic MND (7). Subsequently, others identified a massive expansion of a repeated DNA sequence in a gene named C9ORF72. KCL researchers have shown that RNA of the mutant gene is neurotoxic in cellular and animal studies. This mutation is the most common cause of MND accounting for 20-70% of familial and 5-10% of sporadic MND in Europe.

3. References to the research

1. Shaw CE, Enayat ZE, Chioza B, Al-Chalabi A, Radunovic A, Powell JF, Leigh PN. Mutations in all five exons of SOD-1 cause ALS. Annals of Neurology, 1998; 43:390-394.

2. Sreedharan J, Blair IP, Tripathi VB, Hu X, Vance C, Rogelj B, Ackerley S, Durnall JC, Williams KL, Buratti E, Baralle F, de Belleroche J, Mitchell JD, Leigh PN, Al-Chalabi A, Miller CC, Nicholson G, Shaw CE. TDP-43 Mutations in Familial and Sporadic Amyotrophic Lateral Sclerosis. Science 2008;319:1668-72. DOI:10.1126/science.1154584 (753 Scopus citations)
3. Bilican B, Serio A, Barmada SJ, Nishimura AL, Sullivan GJ, Carrasco M, Phatnani HP, Puddifoot CA, Story D, Fletcher J, Park IH, Friedman BA, Daley GQ, Wyllie DJ, Hardingham GE, Wilmut I, Finkbeiner S, Maniatis T, Shaw CE, Chandran S. Mutant induced pluripotent stem cell lines recapitulate aspects of TDP-43 proteinopathies and reveal cell-specific vulnerability. Proc Natl Acad Sci. 2012;109:5803-8. DOI:10.1073/pnas.1202922109. (38 Scopus citations)
4. Vance C, Al-Chalabi A, Smith BN, Hu X, Sreedharan J, Siddique T, Schelhaas HJ, Kusters B, Troost D, Baas F, De Jong V, Shaw CE. Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on Chromosome 9p13.2-21.3. Brain 2006;129:868-76. DOI: 10.1093/brain/awl030. (217 Scopus citations)
5. Vance C, Rogelj B, Hortobagyi T, De Vos KJ, Sreedharan J, Hu X, Wright P, Nishimura AL, Ganeslingam J, Tripathi V, Smith B, Ruddy D, Al-Saraj S, Al-Chalabi A, Leigh PN, Blair IP, Nicholson G, de Belleroche J, Gallo J-M, Miller CC, Shaw CE. Mutations in FUS, an RNA processing protein, cause familial amyotrophic lateral sclerosis type 6. Science 2009;323:1208-11. DOI:10.1126/science.1165942. (638 Scopus citations)
6. Ruddy DM, Parton MJ, Al-Chalabi A, Lewis C, Leigh PN, Powell JF, Siddique T, Postumus Meyjes E, Frank Baas, De Jong V, Shaw CE. Two families with familial amyotrophic lateral sclerosis are linked to a novel locus on Chromosome 16q. American Journal of Human Genetics 2003;73 360-369. DOI: 10.1086/377157.(58 Scopus citations)
7. Shatunov A, Mok K, Newhouse S, Weale ME, Smith B, Vance C, Johnson L, Veldink JH, van Es MA, van den Berg LH, Robberecht W, Van Damme P, Hardiman O, Farmer AE, Lewis CM, Butler AW, Abel O, Andersen PM, Fogh I, Silani V, Chiò A, Traynor BJ, Melki J, Meininger V, Landers JE, McGuffin P, Glass JD, Pall H, Leigh PN, Hardy J, Brown RH Jr, Powell JF, Orrell RW, Morrison KE, Shaw PJ, Shaw CE, Al-Chalabi A. Chromosome 9p21 in sporadic amyotrophic lateral sclerosis in the UK and seven other countries: a genome-wide association study. Lancet Neurology 2010;9:986-94. DOI:10.1016/S1474-4422(10)70197-6. (76 Scopus citations)

Grants

- 2006-13: MRC Programme Grant, Axonal transport, protein trafficking and neurological disease (CCJ Miller, CE Shaw) - £1,036,427
- 2009-13: MRC, MNDA and Heaton Ellis-Trust, Next Generation Sequencing in Familial ALS (CE Shaw, A Al-Chalabi, J De Belleroche, C Lewis, Shaw Lab) - £1,450,000
- 2009-14: Wellcome MRC Strategic Grant Award RNA Processing proteins and neurodegeneration: exploring mechanisms and modeling disease (CE Shaw, S Pickering-Brown, DW Cleveland, D Mann, J Ule, C Houart, J Rouse, Shaw Lab) - £2,611,447
- 2010-13: MNDA Prize Studentship, Gene-hunting in familial amyotrophic lateral sclerosis associated with fronto-temporal dementia using copy number variation arrays, using exon capture and high-throughput sequencing (CE Shaw, CA Vance) - £87,502
- 2010-13: MNDA Project Grant, Modeling Motor Neuron Disease using induced pluripotential stem cells (S Chandran, I Wilmut, T Maniatis, CE Shaw, Shaw Lab) - £187,532
- 2010-2013: Psychiatry Research Trust PhD Studentship. Developing Cellular models of ALS using induced pluripotent stem cells (CE Shaw, AL Nishimura) - £100,000
- 2010-13: European Union FP7 Programme Grant Euromotor, Genetics of ALS (A Al-Chalabi, CE Shaw) - KCL Component €785,458
- 2012-14: American ALS Association, Project Developing Cellular and Animal Models of mutant C9orf72 mediated ALS-FTD (CE Shaw, RH Brown, P deJong) - USD$300,000
- 2013-15: Vertex Pharmaceuticals, Developing a cellular screening platform to identify small molecule correctors of the TDP-43 pathology (CE Shaw, E Daniels) - USD$415,047

4. Details of the impact

KCL research improves care for patients with familial motor neurone disease (MND): The discovery of new genes has dramatically influenced the care of patients with familial MND and at

risk family members enabling rapid diagnosis, predictive gene testing and pre-implantation genetic diagnosis (PGD). In 1997, KCL researchers identified a novel SOD1 mutation in a family with MND, providing a keenly sought explanation for why the disease affected their family and an opportunity for counselling. In 2010, their son aged 30 developed symptoms raising the spectre of MND. Clinical examination and SOD1 gene testing rapidly confirmed the diagnosis, avoiding months of expensive and often invasive investigations. The same year, their eldest daughter was shown to be a carrier by predictive gene testing. With the input of KCL researchers, the PGD service at Guy's Hospital (a King's Health Partner) was granted the first UK licence from the Human Fertilisation and Embryology Authority (HFEA) to undertake PGD for SOD1 gene (1) and in 2013 she delivered a healthy son free from the fear of developing MND.

KCL's gene discoveries are in widespread use in diagnostic and research laboratories: Since the discovery of SOD1, KCL researchers have worked with the Diagnostic DNA Service at Guy's Hospital, rapidly translating research discoveries into robust clinical tests, helping them set up, optimise and validate their genetic assays as well as interpret unexpected results (2). In 2012, the UK Genetic Testing Network (UKGNT) recommended that all UKGNT Laboratories should provide genetic testing for FUS and SOD1 for MND to their local populations (3). There are currently 75 diagnostic laboratories in 20 countries that test for the SOD1 gene, and approximately 35 laboratories in 12 countries that test for FUS, TDP-43 and C9ORF72 (4).

KCL's database is an invaluable resource for clinicians, researchers, patients and families: Genetic variation is common and not all mutations are pathogenic being able to cause MND. In 1995, KCL researchers launched the ALSOD database as a common source of information on SOD1 mutations. It is continuously updated by registered clinical and research laboratories and now includes a comprehensive account of mutations in all MND genes linked to anonymised clinical data. This enables clinicians to establish whether any variant they have identified is associated with MND. It also gives patients and families general information about MND genetics and specific information on the gene affecting their family, if known. Since 2009, ALSOD has been cited in 389 publications, and has been viewed 842,226 times by 49,563 unique viewers from 152 countries, averaging ~700 visits a day in 2013 (5).

KCL's research promotes international collaboration: Success in the discovery of new MND genes has enabled KCL to lead major collaborative gene hunting efforts. In 2009, the Medical Research Council (MRC) and the Motor Neurone Disease Association (MNDA) funded the use of cutting edge gene hunting technologies including exome capture and next generation sequencing. Early results have identified five new candidate genes (unpublished) but the genes responsible for 30-40% of familial MND cases remain unknown. Prof Shaw leads an international consortium of key MND researchers, working with Dr Benjamin Neale from the Broad Institute at MIT/Harvard (US) to undertake the first meta-analysis of 1,000 familial MND cases. Prof Al-Chalabi leads several European Union-funded international consortia on genetic and environmental causes of sporadic MND ("Euromotor", "ALS-CarE", and "STRENGTH") (6).

KCL's research advances understanding of disease and therapeutic prospects: The discovery of two ALS genes involved in RNA processing (TDP-43 and FUS) has provided novel insights into fundamental disease mechanisms through the generation of novel cellular and animal models. KCL research insights, especially the highly cited papers in Science (2008, 2009), and research developments from a Wellcome Trust and MRC Strategic Grant Award, have led to a collaboration with Vertex Pharmaceuticals, to map novel drug targets and conduct high-throughput compound screening (7).

KCL's research is widely disseminated influencing political and public understanding: KCL's new gene discoveries and novel experimental techniques were widely publicised raising political, professional and public awareness. In 2008, Prof Shaw presented his research findings (Sreedharan J et al. Science 2008) at a press conference in London (8a), resulting in articles in the UK and international media, e.g BBC News (8b) and Reuters (8c). Prof Shaw also communicated subsequent findings (Vance C et al. Science 2009) to the media, e.g. BBC News (8d).

In 2011, Prof Shaw was part of the expert working group for the Academy of Medical Sciences policy report on animals containing human material, examining the scientific, social, ethical, safety and regulatory aspects of research involving animals containing human material (9). He was also the sole scientific advisor to the MNDA in meetings with Prime Minister Gordon Brown in 2008 (10), which led to the MRC committing to an additional £7.5 million on motor neurone disease research over the next five years, to be matched by funds from the MNDA (11).

Prof Shaw has spoken to the Science and Technology Select Committee (2007) (12) on the use of hybrid embryos in research. Evidence from this Report influenced the House of Commons vote in May 2008 which defeated an attempt to ban human animal hybrid embryos (13). He has also spoken to several Parliamentary Groups on MND, Stem Cell and Hybrid Embryo research (2008, 2009). This has contributed to legislation being rewritten and passed into law allowing hybrid embryos to be generated for research into conditions such as MND (14).

5. Sources to corroborate the impact

1. HFEA licence for ALS1 SOD1 (OMIM number 105400) PGD
   http://www.hfea.gov.uk/cps/hfea/gen/pgd-screening.htm
   - Details from Clinical Genetics Group at Guy's Hospital available on request
2. Contact: DNA Laboratory Genetic Service at Guy's Hospital, London (details on request).
3. NHS Directory for Genetic Testing (April 2012)
   http://ukgtn.nhs.uk/fileadmin/_migrated/tt_news/news_files/NHSDirectoryforGeneticTestingV9.pdf
4. Gene testing lab databases (Complete list of laboratories available on request)
   http://www.ncbi.nlm.nih.gov/gtr/tests/?term=SOD1%5Bgene%5D
5. ALSOD website address - http://alsod.iop.kcl.ac.uk/Index.aspx
   - Details of ALSOD website activity - http://alsod.iop.kcl.ac.uk/charts/index.aspx
6. International collaborations
   - Collaboration with the Broad Institute at MIT/Harvard (US): letter available on request
   - Euromotor project - http://www.euromotorproject.eu/
   - ALS CarE - http://www.neurodegenerationresearch.eu/initiatives/2012-joint-transnational-calls/closed-calls/healthcare-evaluation-2012/call-results/als-care/
7. Wellcome Trust and MRC Strategic Grant Award for MND and FTD research
   http://www.wellcome.ac.uk/Funding/Biomedical-science/Funded-projects/Major-initiatives/Neurodegenerative-Diseases-Initiative/WTDV027074.htm
8. Media
   a. Science Media Centre press briefing
   http://www.sciencemediacentre.org/new-clue-to-the-cause-of-motor-neuron-disease-research-published-in-science-2/
   b. BBC News – New clue to motor neurone puzzle (Feb 2008)
   http://news.bbc.co.uk/1/hi/health/7266832.stm
   c. Reuters – Study sheds light on paralysing nerve condition (Feb 2008)
   http://in.reuters.com/article/2008/02/28/us-als-cause-idINL2881494820080228
   d. BBC News - Motor neurone disease 'gene clue' (Feb 2009)
   http://news.bbc.co.uk/1/hi/health/7914652.stm
9. Academy of Medical Sciences – Animals containing human material (2011) -
   http://www.acmedsci.ac.uk/p47prid77.html
10. Contact: Director of Research Development, Motor Neurone Disease Association (details on request).
11. Description of MRC funding call for MND
    http://www.mrc.ac.uk/Fundingopportunities/Calls/MND/index.htm
12. Evidence to Select Committee (2007) on hybrid embryos for MND research
    http://www.publications.parliament.uk/pa/cm200607/cmselect/cmsctech/uc272-i/uc27202.htm
    Full report:
    http://www.publications.parliament.uk/pa/cm200607/cmselect/cmsctech/272/27202.htm
13. BBC ethics guide: http://www.bbc.co.uk/ethics/animals/using/hybridembryos_1.shtml
14. Human Fertilisation and Embryology Act 2008, Section 16: Grant of licence
    http://www.legislation.gov.uk/ukpga/2008/22/section/16